

Remarks/arguments:

Claims 29, previously presented, and 51-70, presented hereby, are pending.

Claims 30-50 are cancelled hereby, without prejudice or disclaimer.

Present claim 51 corresponds to claim 29 rewritten to incorporate subject matter found (in the alternative) in claim 30, as follows:

A homogeneous method for determining the chemosensitivity of cells towards at least one substance in a sample by measuring the apoptosis induced by the at least one substance comprising the steps of:

- adding to the cells at least one marker whose specific binding capability to phosphatidylserine can be detected, wherein the marker is added prior to or essentially concurrently with the at least one substance,
- incubating the cells ~~essentially concurrently~~ with the at least one marker ~~whose specific binding capability to phosphatidylserine can be detected~~ and with the at least one substance, and
- detecting the binding between the marker and phosphatidylserine as a function of time in the sample.

Support for the added (underlined) subject matter is also found in the subject application at page 7, lines 5-6, and pages 7-14 (working examples 1 and 2). Present claims 52-70 correspond to claims 31-49, respectively, rewritten to be dependent on claim 51, directly or indirectly.

Applicant wishes to thank the examiner for acknowledging the §119 foreign priority claim. According to the Office Action, the priority document sent by the International Bureau is missing from the file; and, accordingly, the examiner is obtaining another priority document from the International Bureau. Applicant wishes to thank the examiner, again, for obtaining the necessary priority document, in order to officially acknowledge receipt of the priority document, within the requisite time period.

Claims 29-49 were rejected under 35 USC 102(b) as allegedly anticipated by *Journal of Neuroscience Methods*, 86, 63-69 (1998) ("Schutte"). Reconsideration is requested.

First of all, applicant respectfully disagrees with the opinion of the PTO that the phrase "homogenous method" is not a term of art. On the contrary, "homogenous assay" is a term of art having a well-known meaning. For example, online *Genomics Glossary, Assays and screening*, (URL: <http://www.genomicglossaries.com/content/Assays.asp>) (copy attached) provides (**emphasis in original**):

homogenous assay: These assays require no separation steps. Pipette, incubate, and measure are the only steps required. The reactions occur completely in solution generally without **beads** or **solid phase** attachments to interfere with low affinity interactions. Homogenous assay methods are essential for the throughputs required in drug discovery and for assay miniaturisation. In an homogenous assay, all the components of the assay are present during measurement. The elimination of separation steps is the major advantage of these assays, but this present difficulties because of non-specific measurement of the assay constituents. [Whatman Polyfiltronics. Technical Support, Archives "An introduction to assays"].

This term is also utilized in numerous patent applications and patents including e.g. US 5,876,946 (Burbaum). In fact, it appears in the title of at least 114 U.S. patents, e.g., US 6,498,005 (Nikiforov).

As set forth in Nikifarov (column 2, line 43-column 3, line 10):

I. General Description of Assay Methods

A. General Assay Chemistries

The present invention provides novel methods for assaying a number of different reaction types that would normally require the use of heterogeneous assay formats, but through the use of a novel homogeneous assay format. In particularly preferred aspects, the methods of the present invention typically employ novel assay chemistries that yield reaction products that are independently detectable over and above the reactants used in the reaction, where previously described assays required heterogeneous formats, e.g., reaction followed by separation.

Generally, the present invention uses novel assay chemistries to permit the selective attachment of labeling group to either the product of the reaction of interest or one of the reactants involved in the reaction. In a heterogeneous format, a simple label group may be used which is selectively attached to one of the reactants or the product. The reactants and product are then separated and separately detected. The amount of product produced or substrate used is then determined by virtue of increases or decreases in the amount of label in either the product or reactants, respectively.

In order to provide a homogeneous assay format where the entire reaction mixture is maintained in the same reaction zone or vessel, however, use of a simple labeling group does not suffice, as there is typically no basis for identifying that the detected label originates from product, reactant, or otherwise unincorporated label. In the present invention therefore, the detectable moiety provides a basis for determining where the label originates, and thereby quantitating the amount of either the reactant or the product before or after the reaction of interest.

Accordingly, not only does Nikifarov show that "homogeneous method" is a term of art, the reference definition contrasts a homogeneous assay with a heterogeneous assay, as done in the subject application. As taught in the subject application, at page 5, lines 22-23,

all previous test protocols contain washing steps and are therefore classified as heterogeneous assays,

and at page 7, lines 6-9,

in contrast to the heterogeneous test protocols employed to date, this is a homogeneous test of the "mix and measure" type which enables the immediate measurement of the kinetics of the apoptotic process.

The patentable difference between Schutte's *heterogeneous* method and the *homogeneous* method presently claimed, as well as the advantages of the presently claimed invention, were explained in detail in applicant's Amendment filed March 26, 2004.

As previously explained, in contrast to the presently claimed "homogeneous" method, Schutte discloses a *heterogeneous* method. In accordance with the Schutte method, cells are twice washed with culture medium, in order to remove excess marker, i.e., annexin V-FITC. There is no concurrent incubation as in the presently claimed method. As taught by Schutte, apoptosis is induced by incubating cell cultures with roscovitine or okadaic acid (Schutte, page 65, §2.4). Thereafter, at several points in time, the initial sample is split and aliquots of the cells are incubated with the annexin V-FITC marker (Schutte, page 65, §2.5; figure 3). Consequently, Schutte does not teach detection of the binding of phosphatidylserine and the marker, as a function of time, in the sample.

For anticipation under § 102 to exist, each and every claim limitation, as arranged in the claim, must be found in a single prior art reference. *Jamesbury Corp. v. Litton Industrial Products, Inc.*, 225 USPQ 253 (Fed. Cir. 1985). The absence from a prior art reference of a single claim limitation negates anticipation. *Kolster Speedsteel A B v. Crucible Inc.*, 230 USPQ 81 (Fed. Cir. 1986). A reference that discloses "substantially the same invention" is not an anticipation. *Jamesbury Corp.* To anticipate the claim, each claim limitation must "*identically* appear" in the reference disclosure. *Gechter v. Davidson*, 43 USPQ2d 1030, 1032 (Fed. Cir. 1997) (*emphasis added*). To be novelty defeating, a reference must put the public in possession of the identical invention claimed. *In re Donahue*, 226 USPQ 619 (Fed. Cir. 1985).

As explained, above, Schutte fails to describe a homogeneous method as presently claimed. In that a limitation on the present claims is absent from Schutte, anticipation of rejected claim 29,

and presented claims 51-70, under §102(b) based on Schutte is negated. *Kolster Speedsteel A B, supra.*

Moreover, by teaching use of a *heterogeneous* method, Schutte, in fact, teaches away from the presently claimed "homogeneous" method. "A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." *In re Gurley*, 31 USPQ2d 1130, 1131 (Fed. Cir. 1994). A person skilled in the art reading the teachings of Schutte to use a *heterogeneous assay* "would be led in a direction divergent from the path that was taken by the applicant," i.e., the path of using a *homogeneous assay*.

Present claims 51-70 are further patentable over Schutte, in that the claims are limited to the step of

- adding to the cells at least one marker whose specific binding capability to phosphatidylserin can be detected, wherein the marker is added prior to or essentially concurrently with the at least one substance.

Schutte first cultures the cells in the presence of the "roscovitine" and, thereafter, labels them with the marker "annexin V," after various periods of time (see description figure 3). This is in contrast to the invention of present claims 51-70, whereby, the marker is added prior to or essentially concurrently with the substance. Accordingly, anticipation of present claims 51-70 under §102(b) based on Schutte does *not* exist, because each and every claim limitation, as arranged in the claims, is not found in the reference. *Jamesbury Corp.*

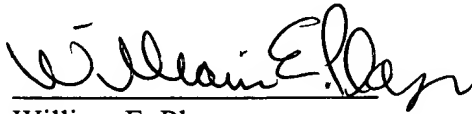
In view of the foregoing, withdrawal of the rejection under 35 USC 102(b) based on Schutte appears to be in order.

Favorable action is requested.

Respectfully submitted,

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Assays & screening

Evolving Terminology for Emerging Technologies

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Last revised August 06, 2004

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*As combinatorial chemistry matures, diversity- oriented synthetic chemists are achieving more structural complexity, tackling compounds with multiple stereocenters and complex natural product- like core structures. Recent advances in multi-component reactions and asymmetric catalysis push the frontiers of effectively populated chemical space. Structurally complex and diverse compound libraries effectively probe biological space for finding initial leads, while targeted, focused libraries enable more rapid lead optimization. **Diversity Oriented Synthesis: Populating Chemical Space**, Nov. 9-10, 2004, Boston MA*

analysis, molecular - innovative: Molecular analysis technologies of interest [to the National Cancer Institute] include those that are entirely novel, or emerging but not currently in broad scale use, or technologies currently in use for one application or set of applications, that are being evaluated for utility for alternative applications. ... Technologies suited for this solicitation, include those that enable the: detection of alterations and instabilities of **genomic DNA**; measurement of **expression** of **genes** and **gene products**; analysis and detection of gene and or cellular products including differential expression, quantitation, **post translational modification**, and function of proteins; identification of exogenous infectious agents in cancer; **assaying** the function of major signal transduction networks involved in cancer. Additionally, technologies that will support molecular analysis *in vitro*, *in situ*, or *in vivo* (by **imaging** or other methods) are suitable. [NCI, Innovative Technologies for the Molecular Analysis of Cancer, 2001]
http://otir.nci.nih.gov/tech/imat_ini.html#inno

Related terms: [Cell biology glossary](#) [cellular resolution](#); [Expression glossary](#) [molecular profiling](#)

assay A set of operations having the object of determining the value of a quantity. In analytical chemistry, this term is synonymous with measurement. [IUPAC Compendium]

Generically a **bioassay** where biological activity is derived; associated with a bioactive effector molecule. Within the **screening** discipline, an assay will probably be robust enough and have the capacity to enable testing of up to 10,000 samples, generally with limited chemical **diversity**. [The precise definition of the following terms varies widely between drug discovery companies. The meanings given here are aligned with the use of the terms within the lead discovery function at GlaxoWellcome. Martin J. Valler, Darren Green "Diversity screening versus focussed screening in drug discovery" Drug Discovery Today 5(7): July 2000]

It could be argued that the rate-limiting factor in biology at the moment is not the speed of assays but devising the assays themselves; that is, establishing new and imaginative ways of measuring biological activity *in vivo* or *in vitro* and then using genetics or biochemistry to use the players - Kim Nasmyth ["Opinions on the potential of yeast biochemical genomics" in "The awesome power of yeast biochemical genomics" Trends in Genetics 16 (2): 49- 51 Feb. 2000]

Narrower terms: Enzyme- Linked Immunosorbent Assay ELISA, force assays, primary assays, secondary and tertiary assays; bioassay, cell assays, high content assays, homogeneous assays, immunoassay, quantitative assays, sandwich assay, single cell metabolism and enzyme assays, "smart" assays; primary assays, secondary assays; **Related terms:** screening

bead assays: The introduction of LEADseeker technology from Amersham Biosciences enabled a huge reduction in the read time for SPA- type assays. It became possible to read an entire 384- well plate in two minutes compared to forty minutes previously. This removed significant 384- well screening bottlenecks but also opened the door for miniaturizing these assays to 1536- well plates, increasing throughput to over 200,000 wells per day. Dr. Jonathan O'Connell, Bristol-Myers Squibb Company, "CLIPR and LEADseeker Imagers for 384 and 1535 LEADseeker Bead Assays" Advances in Assays, Molecular Labels, Signaling & Detection: Profiling PCR June 27- 28, 2002, Washington DC

binding assays: See under force assays

bioassay: A procedure for determining the concentration or biological activity of a substance (e.g. vitamin, hormone, plant growth factor, antibiotic, enzyme) by measuring its effect on an organism or tissue compared with a standard preparation. [IUPAC Medicinal Chemistry]

A bioassay is a single step within a microarray experiment. There are 3 types of bioassays. A **physical bioassay** correspond to wet- lab microarray experimental step. A **measured bioassay** corresponds to a situation after feature extraction has been performed. A **derived bioassay** corresponds to data processing experimental steps. [MGED "bioassay"] <http://www.mged.org/Workgroups/MAGE/bioassay.html>

biochemical assays: Measure how compounds bind to targeted molecules (such as receptors) or how compounds inhibit enzyme activities. CHA High- Content Analysis Market Outlook report, 2004

cell assays, cellular assays: Cell biology is also looking less traditional these days. Companies ... have developed **live cell assays** that fully automate sample handling and quantify cellular characteristics such as motility, proliferation and morphology. The ability to track the behavior of individual cells over time permits data gathering on functional behavior not available in any other kind of assay. This functional assay technology is amenable to high throughput analysis, and therefore can occupy a niche complementary to many proteomic technologies focused on identification of potential therapeutic targets. [CHI Summit Proteomics report]

Can be used for drug **screening** ... some companies are using such assays to gain insights about target function.... assays [can also be used] to get detailed functional information [CHI Breaking Bottlenecks report]

Google = "cell assays" about 1,900 "cellular assays" about 1,130 Aug. 21, 2002

Cellular Assays Help Ease Target- Validation Bottleneck, CHI's GenomeLink 9.1
http://www.healthtech.com/newsarticles/issue9_1.asp

Related term: Microarrays glossary: phenotypic microarray **Narrower term:** live cell assays

cell-based assays: The need for higher quality and quantity of biologically relevant data from primary screening has led to a widespread increase in the use of cell- based assays in HTS. *In vitro* target binding assays do not address drug efficacy and toxicity in a relevant biological context and typically deliver information about one target at a given time. High-throughput cell based screening can provide information on multiple parameters for a given target or multiple target proteins simultaneously in a biologically relevant context. Increasing quality and quantity of output from primary screening is going to be particularly important given the current influx of new targets emerging from genomics with which the industry has little or no past experience. Cell based assays for HTS Intelligent Drug Discovery & Development May 17-18, 2004 Philadelphia PA

Any of a number of assays done in living cells. In the context of high- content screening, researchers typically observe the various effects of investigational compounds on cellular activities (e.g., movement of transcription factors to the nucleus), with the aim of getting functional readouts for the compounds. Key to getting information from cell-based assays are image analysis and image- processing techniques. CHA High- Content Analysis Market Outlook report, 2004

Google = about 2, 780 Aug. 21, 2002; about 9,780 Mar. 22, 2004

Narrower term: high throughput cell based assays

cell based screening assays: The use of cell- based assays has increased in drug discovery so that they are used not only for target validation and secondary screening but for primary high- throughput screening as well. There are many items to consider when choosing which assay format, cell based or biochemical, meets your target screening needs. In addition, one must consider whether to run in a high- throughput format or simply by using an automated workstation approach. This presentation will discuss these considerations and provide three examples of automated cell- based screening assays. "Strategies for Developing Cell-Based Screening Assays" Dr. Lisa Minor, Johnson & Johnson Pharmaceutical R&D *Intelligent Drug Discovery & Development*, May 28- 30, 2003 Philadelphia PA

Related terms: cell assays, cellular assays

Google = about 614 Aug. 21, 2002

cell- based uHTS: The sequencing of the genome presents a proliferation of potential targets for drug discovery efforts. A chemical genomic strategy performs uHTS with many targets in parallel at an early stage in the drug discovery process to identify compounds that can serve as lead structures and as pharmacological tools in target validation. A key component in a successful chemical genomic approach is a uHTS platform with sufficient throughput and flexibility to rapidly test many targets. "Chemical Genomics Using Cell-Based uHTS" Prof. Nina Mohell, Director, Lead Discovery, ACADIA Pharmaceuticals *Chemogenomics/ Chemical Genomics* Nov. 18- 19, 2002, Boston MA

cell free kinase assays: Recently several new cell- free kinase assay technologies have emerged. We have evaluated some of these approaches using small- scale compound screens. Our experiences will be discussed, with particular reference to "generic vs. specific" approaches and the potential benefits of using "counter- screens" to remove false positives. "Evaluation of Kinase Assay Technologies" Mr. Pirthipal Singh, Associate Team Leader, EST- Chemistry, AstraZeneca *Effective Drug Screening: Streamlining Targets- to- Leads, Intelligent Drug Discovery & Development* May 28-30, 2003, Philadelphia, PA

cell free screening: Cell-free screening methods have proven ideal for the discovery of antagonists of membrane tyrosine kinase receptors but fall short in the detection of agonists. Cell-based methods have utility for the discovery of both agonists and antagonists. This presentation will highlight some of the cell-based methods that have been utilized for the screening of membrane tyrosine kinase receptors. Screening for Modulators of Membrane Tyrosine Kinase Activity: Focus on Cell- Based Assays, Lisa Minor, Ph.D., Principal Scientist, Johnson & Johnson, *Cell Based Assays for HTS*, May 17-19, 2004, Philadelphia PA

cell morphology based screens: More than 20 screens have been developed by various groups at Harvard Medical School since we set up an automated fluorescence microscopy- based compound- screen system three years ago. These screens covered both broad and focused biological processes. I will share with you our experience in screen design, hits follow- up, biological target identification, and our current thinking on assay development. "Rethinking Cell Morphology Based Screens" Dr. Yan Feng, Institute of Chemistry and Cell Biology, Harvard Medical School *Target driven chemistry* Mar 17- 20, 2003 Santa Clara CA Molecular Medicine MarketPlace

cellular screens: See cell assays, cellular assays

Google = about 51 Aug. 21, 2002

combinatorial libraries: Combinatorial libraries & synthesis glossary

competitive immunoassays: Rely on the competition between a labeled and unlabeled antigen for a limited number of antibody binding sites. [B. Weigl et al "Novel Immunoassay formats for integrated microfluidic circuits" SPIE BIOS 2000] <http://www.micronics.net/spiebios2000/spie2000novellAformats.htm>

A single antibody is bound to a small molecular weight antigen of less than 10,000 kD. The antibody, at a very low concentration, binds the antigen in the sample. Then a known concentration of antigen is labelled with a detector ... All

remaining antibody sites bind the labelled antigen. The amount of either the bound or free- labeled antigen added to the reaction is measured at the end of the immunological binding reaction. The percentage bound is inversely proportional to the amount of unlabeled antigen. The antibody bound enzyme- labeled antigen is separated at the end of the immunological binding reaction using a secondary antibody coated microplate that specifically binds the primary antibody. The resulting signal is inversely proportional to the amount of antigen in the sample. [Whatman Polyfiltronics, Technical Support, Archives "An introduction to assays"] <http://www.whatman.plc.uk/>

Broader term: immunoassay; **Related term:** competitive PCR

compound risk: Drug Discovery & Development glossary

compound validation: A process to rapidly identify drug candidates with optimal pathway selectivity as well as pharmacology and toxicity profiles. "Pathway Based Drug Discovery and Compound Validation" Dr. Pratik Shah, Chief Business Officer, Kalypsys *Chemogenomics/ Chemical Genomics* Nov. 18- 19, 2002, Boston MA

A process to quickly determine whether a molecule identified in a screen or assay will eventually lead to a drug. If you look at the costs of developing compounds into drugs, the most costly failures result from toxicity or **pharmacokinetic** liabilities rather than from their failure to act on the target. [CHI Breaking Bottlenecks report]

Related terms: Target validation glossary

Conformation-Dependent Immunoassays CDI:

contextual cell-based screening: Gaining a thorough understanding of gene function requires a return to the study of cell biology at the system level. Conventional technologies for investigating cell biology, however, rely on measuring single components independently within populations of cells, often at a single point in time. To improve our understanding of cellular mechanisms — a common goal in drug discovery and development — a systemwide approach can reveal significantly more biological information. Systemwide methods require monitoring multiple events simultaneously in individual living cells in culture or within tissues. Atto's presentation will discuss the application of new single- cell imaging technology to cell- based screening and the importance of viewing cellular events kinetically and spatially to derive contextual biological information. "Contextual Cell-Based Screening" Dr. Joel Jessee, Vice President, Research and Development, Atto Bioscience *Effective Drug Screening: Streamlining Targets- to- Leads, Intelligent Drug Discovery & Development* May 28-30, 2003, Philadelphia, PA

counterscreens: Investigators must develop counterscreens for their assays, with potential deselection criteria including toxicity and suppression of expression from CMV or another promoter. Draft copy: report Workshop on Drug Discovery for Huntington's Disease, Cambridge, MA, February 10- 11, 2001] <http://www.hdfoundation.org/workshop/20010210Abstract.html>

Pharmaceutical researchers typically counterscreen candidate compounds against a limited number of related available targets, sometimes resulting in toxicity problems that involve off- target interactions with other previously unknown proteins in the family. [ActivX Technology "Activity Based Proteomics" <http://www.activx.com/technology.htm>

derived bioassay: See under bioassay

diagnostics: Molecular Medicine glossary

dissociator assays: Proteomics glossary

diversity screening: The drivers behind the current ethos of large- scale diversity **HTS** are rooted in the desire to build an improved hit identification process, and are based on the simple model of testing everything. The key activity over the past five or so years has been scaling: taking the existing model and increasing capacity by application of technology. [Martin J. Valler, Darren Green "Diversity screening versus focussed screening in drug discovery " Drug Discovery Today 5 (7) : July 2000]

drug screening: The proliferation of potential drug targets has resulted in increased screening efforts and put more

pressure on assay development, however it has mostly failed to yield more or higher- quality drug candidates. To reduce the attrition rates at the later stages of the development process, researchers are placing more emphasis on functional assays through high- content screening, carefully choosing the right assay targets, designing target- focused compound libraries, and bringing in informatics and modeling on the front end. The Effective Drug Screening conference will address the latest technologies and applications in high- throughput and high- content screening, assay development and validation, and novel screening approaches. **Effective Drug Screening: Streamlining Targets- to- Leads, Intelligent Drug Discovery & Development** May 28-30, 2003, Philadelphia, PA

Combinatorial chemistry and high-throughput screening have greatly transformed the drug industry. These new technologies had one simple goal in their agendas - to speed up drug discovery and development. As a result of the revolution, a screening group can process 50,000 to 100,000 samples per day compared to 50 to 100 compounds per day a decade ago. Drug discovery at such an unprecedented industrial scale requires the process to be highly effective, efficient, and economic. "Effectiveness, Efficiency, and Economy: The Three Essentials of Drug Screening" Dr. John Wang, Chiron Corp. **Effective Drug Screening: Streamlining Targets- to- Leads, Intelligent Drug Discovery & Development** May 28-30, 2003, Philadelphia, PA

druggable genome: **Drug discovery & development glossary**

ELISA: SEE Enzyme- Linked Immunosorbent Assay

electron microscopy -- drug screening: We present SEMart, a novel electron microscopy (EM) technology that allows observation of fully hydrated samples at atmospheric pressure and room or body temperatures. The technology enables direct imaging of minimally perturbed cells, tissues, and microbes at molecular resolution while avoiding the artifacts associated with sample preparation for EM. The resulting ability to automate electron microscopy opens up a new sphere of high-content drug assays. "SEMart: Electron Microscopy for Drug Screening" Dr. Opher Gileadi, Chief Scientific Officer, Quantomix, Ltd. **Effective Drug Discovery Intelligent drug discovery and development** May 28-30, 2003 Philadelphia, PA

Related terms: **Microscopy glossary**

Enzyme-Linked Immunosorbent Assay ELISA: An immunoassay utilizing an **antibody** labeled with an enzyme marker such as horseradish peroxidase. While either the **enzyme** or the **antibody** is bound to an immunosorbent substrate, they both retain their biologic activity; the change in enzyme activity as a result of the enzyme- antibody- **antigen** reaction is proportional to the concentration of the antigen and can be measured spectrophotometrically or with the naked eye. Many variations of the method have been developed. [MeSH, 1986]

focussed screening: Focussed screening is now well established as a successful **hit** generation strategy. With focussed screening, it should also be possible to use an **assay** that is more appropriate, rather than one that works well at a large scale. [Martin J. Valler, Darren Green "diversity screening versus focussed screening in drug discovery " Drug Discovery Today 5 (7): July 2000]

force assays: Today there is an increased need to improve the selectivity and specificity of nucleic acid and **protein microarrays** in order to detect slightest variations in target molecules, such as **SNPs** and differences protein **phosphorylation**. Measuring the binding and unbinding forces (**tractivity**) of molecular complexes, such as **receptor ligand** pairs or complementary nucleic acid sequences, reveals additional information on the binding complex. This extra information is orthogonal to the affinity measured in conventional **binding assays**, allowing for the discrimination of target molecules, which cannot be distinguished otherwise. However, typical force experiments are conducted sequentially and at the **single molecule** level, which makes it difficult to increase the throughput by several orders of magnitude. Here we present a new C-FIT force assay enabling us to probe large numbers of molecules (>>1010) simultaneously, using a chip format with a built- in differential force **sensor** that is capable of **multiplexing**. This force assay enables us improve the selectivity and specificity of nucleic acid and **protein arrays** significantly and to reduce unwanted cross- reactions. Dr. Hauke Clausen- Schaumann, nanotype GmbH "Highly Parallel Molecular Interaction Force Assays for Proteomics and SNP Detection" **Assays, Molecular Labels, Signaling & Detection: Profiling PCR & Proteins** June 27- 28, 2002, Washington DC

GLP bioanalysis: GLP Good Laboratory Practice and GCP regulated bioanalysis of drugs are a major component of the drug development process and an attractive opportunity for in-sourcing based on both cost savings and time- to-

shelf advantages. Many pre- IND compounds are supported with small-sample-number studies, requiring very fast turnaround to choose between candidates, plan dose levels, and define parameters of next- step studies. Many contract laboratories see these small studies as unprofitable and unattractive and charge a "batch fee" to offset the cost of handling small studies. In addition, many drug candidates do not proceed to IND early development. For these reasons and many others early development is a particularly attractive in-sourcing opportunity. In addition, rapid turn around of First in Human (FIH) samples can facilitate the titration of individual patients, depending on the exposure of a drug for a particular patient, which has several key advantages. Finally, the failure of many high- throughput discovery and automation approaches over the last two decades to produce successful drugs has lead to the realization that traditional drug discovery and drug development offer a better return on investment. As a result many small, mid- sized, and large pharmaceutical companies are re-investing, or increasing their investment in internal GLP bioanalysis in addition to many other traditional drug development and discovery approaches. The growth in this area has driven a need to develop services for the industry that smooth the transition to in- sourcing.

Contract laboratories have a stake in supporting the growth of internal GLP laboratories to support small, unprofitable studies and in providing the variety of services that new GLP labs will require to begin in- sourcing. There are many examples to be found of such business opportunities. This opens up the opportunity for contract laboratories to demonstrate their expertise and build a strong partnership with pharmaceutical companies that facilitates their participation for later-stage large study support. Finally, no formal guidelines have ever been presented to the industry for the startup phase of the GLP laboratory. **GLP BioAnalysis: Building a Lab from the Inside Out, Sept. 21-22, 2004, Baltimore MD**

genomic assays: Entering the post- genome era with an increasing amount of sequence data available in databases, a complex matrix of possibilities is opened for genome research. To address this vast arena of genomic questions, we designed a flexible probing tool based on DNA microarrays. The technology was designed to handle all kinds of genomic assays like **expression profiling, genotyping, or resequencing** for any given organism with the only prerequisite being that sequence data are available. The arrays are *in-situ* fabricated, hybridized, and analyzed within one single bench top instrument. The whole assay itself is defined by a software file (Digital Array) that holds the sequence data for all DNA- probes that will be put onto the array. New **microarrays** can be developed by altering the composition of these file. Dr. Peer F. Stähler, febit ag "Geniom® Technology: Exploring Nature's Plasticity with a Flexible Probing Tool" **Microarrays Through Macroresults: Advancing Drug Development April 29- May 1, 2002 Boston, MA**

high content analysis: It is the goal of the 2005 meeting to establish a dialogue between the technology end- users at an "end- users only" pre- conference forum, as well as facilitate a dialogue between the end- users and the technology providers. The meeting will further feature case studies of applications in primary and secondary drug screening, ADME/Tox, target validation and functional genomics, as well as a variety of new applications. **High Content Analysis, Jan. 24-28, 2005 San Francisco, CA**

For purposes of this report, this term is used to describe the convergence between cell- based assays, high- resolution fluorescence imaging, automation and advanced image processing and analysis software. CHI **High- Content Analysis Market Outlook** report, 2004

Google = about 420 July 14, 2004

Related/equivalent terms: high content assays, high content screening

high content assays:

Google = about 164 July 14, 2004

high-content cellular analysis: By using multiple fluorescent reporter systems, combined with high- resolution imaging and high- throughput image analysis, researchers can observe multiple intracellular events in individual cells. High- content screening (HCS) enables functional analysis of target and pathway modulation in living cells by potential drug compounds. Availability of high- content cellular information at early stages in drug discovery process will improve the quality of targets, hits, and leads; reduce late- stage attrition; and shorten time and cost of drug development. **High Content Analysis, Jan. 24-28, 2005 San Francisco, CA**

Google = about 122 Aug. 6, 2004

high-content screening HCS:

Google = about 4,100 July 14, 2004

Related/equivalent term: high content analysis

high throughput microscopy: Microscopy glossary

High Throughput Screening HTS: Process for rapid assessment of the activity of **samples** from a **combinatorial library** or other compound collection, often by running parallel **assays** in plates of 96 or more wells. [IUPAC Combinatorial Chemistry]

Traditionally describes the running of a large-scale assay campaign looking at the effects of a large number of compounds on a biological target. CHI High- Content Analysis Market Outlook report, 2004

Broader term: screening

Narrower term: ultra high throughput screening

Related terms: high content analysis, high content screening, throughput

high throughput cell based assays: We have developed a system for high- throughput cell- based assays. The system was used to investigate genes' function and their roles in signaling pathways. Combining gene function information with results from gene expression analysis, regulatory sequence analysis, and literature mining, we were able to identify gene networks consisting of potential drug targets. A database and a web interface have been developed to enable efficient data mining. The system has become an important tool for target identification and prioritization. "From Gene Networks to Drug Targets" Dr. Jian Zhu, Novartis Institute of Biomedical Research, Novartis AG **Systems Biology: Pathways to Drug Development** June 18- 19, 2003, San Diego, CA

hit: Library component whose activity exceeds a predefined, statistically relevant threshold. [IUPAC Combinatorial Chemistry]

A molecule with robust dose response activity in a **primary screen** and known, confirmed structure. The output of most **screening**. [The precise definition of the following terms varies widely between **drug discovery** companies. The meanings given here are aligned with the use of the terms within the lead discovery function at GlaxoWellcome. Martin J. Valler, Darren Green "Diversity screening versus focussed screening in drug discovery" Drug Discovery Today 5 (7): July 2000]

Related terms: High Throughput Screening HTS, hit optimization library, lead discovery, screening. Narrower term: integrated hit identification, progressible hit

hit enrichment: The cyclin-dependent kinase 2 (CDK2) is one of the most important targets in current cancer research. A number of CDK2 protein- inhibitor complexes are available in the PDB, revealing considerable protein flexibility within the ligand-binding pocket. We have applied different virtual screening protocols, including standard sequential FlexX docking in different CDK2 X-ray structures, docking with pharmacophore constraints using FlexX- Pharm, and docking into an ensemble of ligand- binding pockets using the FlexE module. We will describe the results in terms of hit enrichments for a data set comprising known CDK2 inhibitors from the literature and compounds without any reported kinase activity from the world drug index. "The Effect of Different Virtual Screening Protocols on Hit Enrichment for Cyclin- Dependent Kinase 2" Dr. Hans Briem, Schering AG **Structure- based Drug Design: April 28- 29, 2003, Cambridge MA**

hit optimization library: Combinatorial Libraries & synthesis

hit to lead: Improving the success rate in drug discovery requires stringent selection and development of the most promising hits generated by HTS. Bridging the gap between hit identification and entry into a full lead optimization program is critical. Decisions made at this early stage have costly implications further downstream. Many of the major

pharmaceutical companies have recognized the need to establish hit- to- lead groups to rigorously select appropriate candidates and generate the most promising lead series. Successful lead generation requires an in-depth assessment of chemical integrity, synthetic accessibility and functional behavior as well as ADME features in parallel. Standardizing and utilizing such a set of lead criteria allows for better and more timely decisions to be made at this critical juncture in the drug discovery process. **Hit to Lead: Streamlining Lead Generation to enhance downstream success: Intelligent Drug Discovery & Development May 17-18, 2004 Philadelphia PA**

homogeneous assay: These assays require no separation steps. Pipette, incubate, and measure are the only steps required. The reactions occur completely in solution generally without **beads** or **solid phase** attachments to interfere with low affinity interactions. Homogeneous assay methods are essential for the throughputs required in drug discovery and for assay miniaturisation. In any homogeneous assay, all the components of the assay are present during measurement. The elimination of separation steps is the major advantage of these assays, but this presents difficulties because of non- specific measurement of the assay constituents. [Whatman Polyfiltronics. Technical Support, Archives "An introduction to assays"] <http://www.whatman.plc.uk/>

image analysis/image processing: In the context of high- content screening, these efforts involve drawing conclusions from image- based data, typically from living **cells** that have been exposed to compounds of interest. Analyzing such images can be challenging for many reasons, including the transient nature of cellular events and the fact that image- processing **algorithms** are still not robust enough for certain important applications (e.g., **pattern recognition**). [CHI High- Content Screening report, 2002]

Related terms: Molecular Imaging glossary

immunoassay: A **ligand**- binding assay that uses a specific **antigen** or **antibody**, capable of binding to the analyte, to identify and quantify substances. The antibody can be linked to a radiosotope (radioimmunoassay, RIA), or to an enzyme which catalyses an easily monitored reaction (**enzyme- linked immunosorbent assay, ELISA**), or to a highly fluorescent compound by which the location of an antigen can be visualized (immunofluorescence). [IUPAC Compendium]

Only method possible for small molecular weight **antigens**, such as steroids, drugs, lipids, and peptides. There are three basic components in any immunoassay, the antigen to be detected and/or quantified, a specific antibody to this antigen, and a system to measure the amount of the antigen in the sample. The separation at the end of the immunological reaction uses a microplate. [Whatman Polyfiltronics. Archives "An introduction to assays"] <http://www.whatman.plc.uk/>

Narrower term: competitive immunoassay **Related term:** ELISA

immunometric assay: See sandwich assay

integrated hit identification: The ever increasing need for high quality lead molecules against a growing number of targets is a challenge to existing high throughput hit identification methods. The emphasis on quality requires hits that are potent, as well as chemically amenable to modifications, with good physico- chemical and specificity profiles. At Ariana, we have developed an integrated cheminformatics platform that combines virtual screening, in- silico ADME-T profiling using Artificial Intelligence methods, and experimental validation. Examples will be presented. "Integrated Hit Identification Platform Combining Virtual Screening, In- Silico ADME-T Prediction and Experimental Validation" Dr. Mohammad Afshar, Ariana Pharmaceuticals **Cheminformatics: Intelligent Drug Discovery May 28- 30, 2003 Philadelphia PA**

kinase inhibitor assays: Many different approaches can be taken to developing assays for screening of kinase inhibitors, and issues such as the size of the compound library to be screened, the required throughput, and cost must be taken into consideration. We have developed several assays for tyrosine and serine/threonine kinases using both ELISA and homogeneous solution phase technologies. In addition, we have developed a high throughput cell based assay for evaluation of inhibitors of a receptor tyrosine kinase. The advantages, disadvantages, and comparative performance of various approaches will be discussed. Development of Kinase Inhibitor Assays, Dr. Laura DeForge, Scientist, Assay & Automation Technology, Genentech, Inc. **Protein Kinase Targets: Strategies for Drug Development June 10-11, 2003, Boston MA**

kinase selectivity panel: The use of a kinase selectivity panel to direct kinase inhibitor series selection for medicinal chemistry will be presented. The panel is invoked immediately after confirming HTS hits and used throughout lead optimization. The early availability of potency and selectivity data alongside purity and structure information has enabled us to intelligently prioritize chemistry exploration of the large numbers of hits from primary screens. The general implementation and use of the kinase selectivity panel, as well as specific examples of successes, will be discussed. The Utilization of a Kinase Selectivity Panel in the Steering of Hit to Lead Programs, Debra Gallant, Research Investigator, High Throughput Biochemistry, Millennium Pharmaceuticals, Inc. **Protein Kinase Targets: Strategies for Drug Development** June 10-11, 2003, Boston MA

lead: A representative of a compound series with sufficient potential (as measured by potency, selectivity, pharmacokinetics, physicochemical properties, absence of toxicity and novelty) to progress to a full **drug development** programme. [The precise definition of the following terms varies widely between drug discovery companies. The meanings given here are aligned with the use of the terms within the lead discovery function at GlaxoWellcome. Martin J. Valler, Darren Green "Diversity screening versus focussed screening in drug discovery" Drug Discovery Today 5 (7): July 2000]

Related term: hit

lead discovery: The process of identifying active **new chemical entities**, which by subsequent modification may be transformed into a clinically useful drug. [IUPAC Medicinal Chemistry]

Related terms: drug discovery, hit, lead generation, lead discovery library, lead optimization, screen

lead discovery library: **Combinatorial Libraries & synthesis**

lead generation: Strategies developed to identify compounds which possess a desired but non- optimized biological activity. [IUPAC Medicinal Chemistry]

The key challenge of our industry is that of improving innovation and productivity at reasonable cost. The exploitation of the human genome for drug discovery and the resulting increased complexity have created bottlenecks and opportunities for improvement. The successful implementation of our Chemical Biology Strategy will be illustrated in the context of integrated new technologies, improved processes and optimal knowledge sharing through industrialization. Examples of increased productivity will be described. "Enhancing Innovation & Productivity in Lead Generation", Dr. Daniel Schirlin, Aventis D&A **Intelligent Drug Discovery & Development**, May 28- 30, 2003 Philadelphia PA

Related terms: drug development, hit, lead discovery, lead optimization

lead identification: Chemistry's role in the early phase of drug discovery continues to evolve, with many exciting new approaches providing enhanced opportunities in target, hit, and lead identification. Chemical genetics approaches allow for contributions to target identification and validation, while virtual screening, affinity methods, and HTS analysis provide opportunities for hit identification. Predictive methods can highlight potential DMPK issues, and computational approaches that relate structure to biology have potential application in targeted design and compound acquisition. "The Changing Nature of Early-Phase Discovery Chemistry in the Pharmaceutical Industry" Dr. James R. Damewood, Jr., AstraZeneca Pharmaceuticals LP **Target driven chemistry track** Mar 17- 20, 2003 Santa Clara CA **Molecular Medicine MarketPlace**

lead optimization: The synthetic modification of a biologically active compound, to fulfill all stereoelectronic, physicochemical, pharmacokinetic and toxicologic required for clinical usefulness. [IUPAC Medicinal Chemistry]

The new lead optimization paradigm demands that companies move to parallel processes that evaluate binding affinity, ADME, drug properties, etc. earlier in the process in order to cut the time and costs lost in failed leads. It also brings new challenges and complications to the field. With the emergence of new technologies to help better identify the most promising leads a critical issue remains the validation and acceptance of these methods by regulatory agencies, as well as having the ability to run in parallel with other techniques in order to accelerate lead selection decisions. This meeting covers the crucial issues, implications, and strategies that allow you to employ new ways of reaching these goals faster, better and more economically. **Smarter Lead optimization: Intelligent drug discovery and development** May 28- 30, 2003, Philadelphia, Pennsylvania

Fueled by the need to bring down the cost of drug discovery and development, a major shift is occurring in how pharmaceutical companies evaluate drug leads. Whereas researchers used to begin by looking at affinity and potency, a genomics/informatics- based research culture is growing and starting to impinge on the classical mode. Companies are now concentrating on determining potential drugs leads' ADMET (absorption, distribution, metabolism, excretion, and toxicological) properties and manufacturability. CHI Advances in Lead Optimization report, 2003

Related terms: drug development; Pharmacogenomics glossary ADME, toxicogenomics; **Narrower term:** parallel optimization

lead prioritization:

lead selection: See lead discovery

lead validation: With no shortage of **drug targets**, increasing emphasis is being placed on lead validation. One key challenge is developing **high throughput screens**.

Related term: target validation.

live cell assays: Can be used to obtain functional information on a wide variety of cellular effects, including **apoptosis**, proliferation, differentiation, migration and protein secretion. Enables a better understanding of protein functionality in normal and diseased states. [CHI Summit Proteomics report]

massively parallel: Many (assays or other procedures) at once.

Related term: Gene amplification & PCR glossary multiplexing

measured bioassay: See under bioassay

medicinal chemistry: Drug discovery & development glossary

microfluidics based assays: Microfluidics-based assays have been deployed throughout the drug discovery process from assay development for novel enzymes through to lead optimization of pre- clinical drug candidates. One of the typical hallmarks of microfluidics applications is the overall higher quality of the data compared with microplate- based formats. Microfluidics- High Quality Screening From Targets to Leads, Seth P. Cohen, Ph.D., Director: Application Sciences ,Caliper Life Sciences, Cell Based Assays for HTS, May 17-19, 2004, Philadelphia PA

miniaturized uHTS: The application of **confocal detection** resulting in multiparameter data sets improves data reliability enormously when extracting and combining the suitable result parameter. The increased data robustness enables one to perform low- threshold "sensitivity screening" runs that significantly help reduce the number of false negatives and enable accessing weak molecular interaction screening. In addition, multiparameter analysis opens the door to efficient approaches to false- positive selection by multiparameter autofluorescence filtering and detection of systematic errors. Together with readout **multiplexing**, confocal detection screening gives the highest precision in **hit** selection from primary **uHTS**, which will be discussed on case studies. Dr. Dirk Ullmann, Evotec OAI , "Sustainable Data from Miniaturized uHTS: Efficient Approaches in Reduction of False Positives and False Negatives" Advances in Assays, Molecular Labels, Signaling & Detection: Profiling PCR June 27- 28, 2002, Washington DC

Narrower term: Ultra high throughput screening uHTS. **Related terms:** Microscopy glossary confocal microscopy

NMR based screening: NMR screening has been combined with a variety of complementary methods- such as virtual screening, HTS, **combinatorial chemistry**, and X-ray crystallography - to carry out directed searches for novel medicinal chemistry leads. This presentation describes the successful application of the SHAPES strategy (a ligand- based method for NMR screening of small, druglike molecules) and SBDD to discover and optimize leads for a variety of targets, including kinases (e.g., Jnk3) and the fatty acid binding protein ALBP. "Combination of NMR Screening with Structure- Based Drug Discovery" Dr. Christopher Lepre, Vertex Pharmaceuticals Inc. Structure- based Drug Design: April 28- 29, 2003, Cambridge MA

Related terms: [NMR & X-ray crystallography glossary](#)

organotypic models: Carl [Westmoreland] returned to the platform to look at the changing definitions of organotypic models, which were once considered to be whole isolate organs or parts thereof. The development of spheroids and other complex cell culture models has expanded the scope of this definition. In turning to look at the future, he outlined the principle challenges in industrial toxicology in the adoption of organotypic models in the chemical, pharmaceutical and cosmetics sectors. In Vitro Toxicology Society, Autumn Meeting, Nov. 2003, Nottingham UK

parallel optimization: The first small molecule agonists of the Melanocortin-1- Receptor will be presented. These compounds were discovered in a very short time by a small team of chemists by the systematic use of parallel synthesis and by optimizing in parallel for potency, selectivity, and pharmacokinetics properties. "Parallel Optimization in the Discovery of Potent and Selective Small Molecule Agonists of the Melanocortin 1 Receptor"

Dr. Timothy Herpin, Senior Research Investigator, New Lead Chemistry, Bristol- Myers Squibb Company [Smarter Lead optimization: Intelligent drug discovery and development May 28- 30, 2003, Philadelphia, Pennsylvania](#)

pharmacology and drug discovery: In drug discovery the job of the pharmacologist is to provide timely, meaningful data to guide the medicinal chemist's decision on what to make next. These data are usually provided to the chemist in the abbreviated form of parameters in simple models of drug action and biodistribution. Key factors governing the choice, design and analysis of bioassays and the value of the parameters abstracted will be discussed with examples from GPCR- targeted research. "Optimizing The Dialogue Between Medicinal Chemists and Pharmacologists" Nigel Shankley, Johnson & Johnson Pharmaceutical Research [Target driven chemistry Mar 17- 20, 2003 Santa Clara CA](#)
Molecular Medicine MarketPlace

phenotypic screening: The systematic classification and characterization of phenotypes is essential for ultimately mapping the genes responsible for normal and abnormal development and physiology. In any search for mutations or altered functional expression, identification depends on phenotypic screening and its ability to detect variation from normal. The challenge is to develop efficient, systematic and comprehensive phenotypic screening procedures and tools that will permit comparison between laboratories, temporally, and between different strains of mice. This is a necessary step before utilizing chemical or other mutagenesis methods to produce large numbers of mutant mice for the investigation of normal and abnormal development and physiology. ... a primary focus of this program is the development of high throughput phenotyping assays or tests that could efficiently, rapidly, and systematically be used to screen anywhere from 5,000 to 20,000 mice per year for alterations in cardiovascular, pulmonary, hematologic or sleep physiology. This could include, but not be limited to, biochemical surrogate markers, noninvasive imaging modalities, microarray analysis, or indicator screens. Another goal is to develop new phenotyping techniques or methods for heart, lung, blood, and sleep disorders that would accelerate the emergence of new concepts and improve our understanding of structural, metabolic, and functional relationships in cardiopulmonary, and blood systems. Development of mouse phenotypic screens for heart, lung, and blood diseases, National Heart, Lung and Blood Institute, NIH, US, Apr. 13, 1999, Request for Application <http://grants1.nih.gov/grants/guide/rfa-files/RFA-HL-99-010.html>

photoaptamer- based assays: Are in development for **candidate proteins** and are being integrated into a single, **multiplexed** array to allow for the simultaneous measurement of proteins of interest. SomaLogic intends to use these Aptamer Arrays for the analysis of body fluids and tissues to diagnose illness and/ or predict wellness by discovering the specific patterns of protein concentrations associated with particular diseases, i.e., disease- specific protein signatures. By examining these profiles from large numbers of subjects, researchers will uncover protein signatures, unique patterns of protein concentrations associated with clinically relevant parameters such as the presence of a disease, probability of response to a particular pharmaceutical, or the extent of response following treatment. "Photoaptamer- Based Protein Detection for Expression Levels of Disease Markers" Dr. Joe Heilig, SomaLogic, Inc. [Gene Functional Analysis Feb. 28 - Mar. 1, 2002 Santa Clara CA](#)

physical bioassay: See under bioassay

predictive e-screens: " Libraria has captured exhaustive public domain SAR on entire gene family targets with a proprietary technology platform that helps one better identify valuable novel compounds than would otherwise be possible. Predictive e-screens were developed to rationally prioritize molecules for synthesis or purchase in an empirically driven approach based on huge amounts of target- specific information, including all major sources of public information. Three successful proofs -of- concept where novel, patentable chemotypes for kinase inhibition were rapidly discovered will be disclosed for the first time. "Leveraging Exhaustive Gene Family- wide SAR with Predictive e-Screens for Data- Driven Drug Discovery" Dr. Barry A. Bunin, Libraria, Inc. [Molecular Medicine Marketplace: Target Driven](#)

Chemistry Mar. 17-21, 2003, Santa Clara CA

primary assay: Assays of drugs done on a single **target** or small groups of targets. [CHI Breaking Bottlenecks report]

primary screening: High- content screening (HCS) technologies are finally approaching the throughput, automation, robustness, and assay development capabilities necessary to handle primary screening. HCS provides efficacy information in a cellular environment which is more predictive of how the drug may behave in humans. It also allows researchers to study targets that are intractable using conventional in vitro assays. Availability of high- content information in primary screening promises to increase the confidence in hits and reduce the need for secondary screens, leading to lower cost and time of drug development. **High Content Analysis, Jan. 24-28, 2005 San Francisco, CA**

Primary screening, which is higher throughput than **secondary screening**, typically seeks to identify which compounds bind to targets of interest, to what degree of affinity. In primary screens researchers may seek to determine what compounds bind to and inhibit targets of interest. CHI High- Content Analysis Market Outlook report, 2004

progressible hit: A representative of a compound series with activity via an acceptable **mechanism of action** and some limited **structure activity relationship**. The precise definition of the following terms varies widely between drug discovery companies. The meanings given here are aligned with the use of the terms within the lead discovery function at GlaxoWellcome. Martin J. Valler, Darren Green "**Diversity screening versus focussed screening in drug discovery**" Drug Discovery Today 5(7): July 2000]

Related term: **Combinatorial libraries & synthesis glossary** **chemistry space**

quantitative assays: Standardization of assays used to quantitate viral load or gene expression has become an issue of concern within the clinical setting. This presentation will examine the current status of quantitative assays with regards to standardization, optimal requirements for assay standardization, and the clinical implications of standardization. "Establishing Standardization of Quantification" Dr. H. James Hnatyszyn, Bayer Healthcare **Eighth Annual Gene Quantification, June 5- 6, 2003 Baltimore MD**

random screening: A staple of the pharmaceutical industry for many years. Now largely replaced by varying combination of **combinatorial chemistry** and/or **rational drug design**.

Related terms: **diversity screening, focussed screening** **Broader terms:** **screen, screening**

sandwich assay: The antigen is "sandwiched" between the two antibodies, one is attached to the solid phase, and the other is labelled with an enzyme. The amount of solid phase antibody and enzyme conjugated antibody are in a higher proportion than the amount of antigen in the sample. The result is an assay that produces a signal that is proportional to the amount of antigen in solution. [Whatman Polyfiltronics. Technical Support, Archives "An introduction to assays"] <http://www.whatman.plc.uk/>

screen: An optimized, streamlined **assay** format with characterized robustness to diverse chemical types and conditions such that testing of 10,000 **samples** is both feasible and cost effective. The spectrum of low- throughput **screening** (10,000 50,000 assay points) medium- throughput **screening** (50,000 100,000 data points) and high- throughput **screening** (100,000 500,000 data points) can be defined. The scale of implementation of a given screen is greatly influenced by format, application of technology (e.g. automation), time and resource constraints. [The precise definition of the[se] terms varies widely between drug discovery companies. The meanings given here are aligned with the use of the terms within the lead discovery function at GlaxoWellcome. Martin J. Valler, Darren Green "**Diversity screening versus focussed screening in drug discovery**" Drug Discovery Today 5(7): July 2000]

Related term: **screening.**

screening: Pharmacological or toxicological screening consists of a specified set of procedures to which a series of compounds is subjected to characterize pharmacological and toxicological properties and to establish dose- effect and dose- response relationships. [IUPAC Tox]

The use of *in vitro* biochemical assays, or tests, to detect compounds which modulate the activity of a target (i.e., **enzyme inhibitors**, **receptor agonists** or **antagonists**). [Oxford Molecular]

While drug screening is often talked about in the context of achieving **hits**, it is useful to note that the *Oxford English Dictionary* definition of screening specifies that this is "esp. for the detection of unwanted attributes or objects".

Narrower terms: diversity screening, focussed screening, HTS High Throughput Screening, synthetic lethal screening, Ultra High Throughput Screening UHTS; Targets glossary target screening Not the same as screening in Molecular Medicine glossary **Related terms: assay, I.R. Thermography**

secondary assays (and tertiary assays): Undertaken after primary screening has identified "hit" compounds against **targets**, are more complicated - and time-consuming - tests of a drug and include **ADME/Tox** (absorption, distribution, metabolism, excretion/toxicology) studies (e.g., done on mice or rats). Test a drug against more than one target, complicated and time- consuming, so they have not been considered practical for use in very early drug development.... The secondary and tertiary assays tell you more biology. ...Typically, secondary and tertiary assays are more comprehensive, but they also take longer, and they are more complex and less reproducible. [CHI Breaking Bottlenecks report]

secondary screening: As the primary screening technologies are becoming increasingly automated and high-throughput, the drug discovery bottleneck is shifting downstream towards secondary screening and lead optimization. This is the area where researchers had the most experience with High Content Screening. The high-content cellular information on lead specificity, bioavailability, and ADME/Tox allows researchers to prioritize leads with more confidence and impact the bottom line by reducing late- stage attrition. *High Content Analysis, Jan. 24-28, 2005 San Francisco, CA*

Secondary screening, which is lower throughput than **primary screening**, seeks to provide more detailed information about compounds than just their binding affinity. For example, secondary screens may shed light on mechanism of action and other parameters. CHI High- Content Analysis Market Outlook report, 2004

single cell metabolism & enzyme assays: Ultrasensitivity glossary

small molecule screening: The basic goal of small- molecule screening is the identification of chemically 'interesting' starting points for elaboration towards a drug. A number of innovative approaches for pursuing this goal have evolved, and the right approach is dictated by the target class being pursued and the capabilities of the organization involved. A recent trend in high- throughput screening has been to place less emphasis on the number of data points that can be produced, and to focus instead on the quality of the data obtained. Walters WP, Namchuk M., Designing screens: how to make your hits a hit. Nature Reviews Drug Discovery 2003 Apr;2(4): 259- 266

"smart" assays: May be operationally defined as a **screening** system that by its very operation conveys information about new chemistry or biology of "hits" in the system. For example, assays of interest to promote may couple the use of a cloned and expressed **target protein** or a nucleic acid sequence in tandem with a chemical or biosynthetic process that generates molecules for further study. Alternatively, the use of genetically definable yet underexplored organisms such as yeast, Drosophila, or C. elegans, production of expression vectors that may operate only in the presence of a compound with the desired properties, development of detection techniques based on novel patterns of **molecular recognition**, or strategies that require the operation of a particular molecular target to be a basis for **detection** would all examples. [NCI, CANCER DRUG DISCOVERY: DIVERSITY GENERATION AND SMART ASSAYS, RFA: CA-97-006, May 9, 1997] <http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-97-006.html>

structural chemistry- driven in- vitro screening: Over the last few years, the utilization of **protein structural** information in drug discovery research has matured and is today applied throughout the process, ranging from **genomics**- derived **target identification** and selection to the final design of suitable drug candidates. An especially powerful methodology has arisen from the clear synergies of the combination of target structural information with **combinatorial chemistry**. Several **structural genomics** initiatives have recently been started and are now generating 3-D structures of target molecules at an unprecedented rate that will provide a wealth of novel information that can be utilized for **rational drug design**. Dr. Martin Norin, Biovitrum "Structural Chemistry- Driven *in- vitro* Screening" *Impact of Genomics-on-Medicine* May 13- 14, 2002, Munich, Germany

structural screening: The discovery of novel drug leads at Astex Technology is driven by the company's unique structural screening approach to **lead discovery**, which utilizes protein crystal structures to detect the binding of **small-molecule** fragments. Using high- capacity **virtual screening**, fragmentation of known drugs, and **ligands** for related **targets**, many hundreds (to potentially thousands) of fragments are identified and prioritized for structural screening using the company's proprietary **X-ray crystallography** technologies. Coupling **virtual screening** with structural screening allows both the routine identification of efficiently binding fragments and their optimization and is rapidly iterated using library enumeration and high- capacity protein- fragment structures. This informatics-based approach results in a powerful process for rapid structure- based **lead generation**. Dr. Robin Carr, Astex Technology Ltd. "The Role of High-Throughput X-ray Crystallography Compared to High- Throughput Screening in Modern Lead Discovery" **Structure- Based Drug Design** Apr. 18- 19, 2002 Cambridge MA

structure based *in silico* assays: Protein Mechanics has developed a novel structure- based platform to accelerate key aspects of the drug discovery process, applying a cross- disciplinary approach to simulate, *in silico*, molecular interactions correctly, efficiently, and robustly. Our technology platform incorporates fundamental principles of physics, biomechanics, and computational chemistry to perform predictive molecular experiments through accurate simulation of physical laws. By performing these *in silico* assays, Protein Mechanics leverages low capital cost and high productivity to accurately determine the dynamic structure of protein co- complexes and thereby accelerate critical drug discovery steps such as lead optimization. "Better Drugs through Physics: How the Fundamental Principles of Physics and Biomechanics Apply to Structure-Based Drug Design" Dr. Michael Sherman, Protein Mechanics, Inc. **Molecular Medicine Marketplace Business Strategies track** Mar. 17- 18, 2003, Santa Clara, CA

structure based screening: Structure- based screening combines the power of NMR spectroscopy, automatic docking, and X-ray crystallography and provides the means to apply structural information (NMR, modeling, and X-ray) early in the projects to identify hits, select targets, and optimize the hits in terms of their affinities and specificities. Some recently developed novel screening techniques to perform site- specific screening will be discussed with the emphasis on the development of new drugs for the treatment of diabetes and obesity. "Structure- Based Screening and Design in Drug Discovery" Dr. Mats Wikström, Biovitrum **Structure- based Drug Design**: April 28- 29, 2003, Cambridge MA

structure based NMR screening: NMR-based methods of screening of drug discovery targets have recently emerged as an alternative and complementary tool to conventional high- throughput bioassay- based screening. We have used structure- based NMR screening approaches (SbN) to identify druglike small molecule hits from customized libraries. NMR- detected hits are turned into leads through chemical optimization that is guided by 3-D structural data. While chemistry on SbN hits can be aided by X-ray crystal structures of ligand- target complexes, such complexes are often difficult to crystallize. We have developed novel tools (SDILICON and JSURF) that utilize the data generated in the NMR screen to rapidly provide an accurate structural representation of protein- ligand complexes under conditions that are not favorable to traditional structural work. We discuss the principles of SbN for lead discovery, then illustrate its application to several drug discovery targets. "Structure- Based NMR Screening Applied to Drug Discovery Targets" Dr. Daniel Wyss, Section Leader, Structural Chemistry, Schering- Plough Research Institute **Effective Drug Screening: Streamlining Targets- to- Leads, Intelligent Drug Discovery & Development** May 28-30, 2003, Philadelphia, PA

synthetic lethal screening: Functional genomics glossary

target, target characterization, target discovery: Targets glossary

target discovery *in silico*: In silico & molecular modeling glossary

target validation, target validation technologies: Targets glossary

tertiary assays: See secondary assays (and tertiary assays)

throughput: Output or production, rate at which something can be processed.

Narrower terms: HTS High Throughput Screening, Ultra High Throughput Screening UHTS

tissue engineering: Biomaterials & Bioengineering glossary

tissue microdissection: Cells & cell biology glossary

tissue models: [Biomaterials glossary](#)

Related term: [organotypic](#)

toxicity testing: An important part of the drug- **lead- optimization** process in which investigational compounds are tested for their potential to cause side effects. CHA, Cambridge Healthtech Advisors [Model Animal Systems: Emerging Applications and Commercial Opportunities in Drug Discovery and Development](#), report, 2004

Both animal models and cellular assays are utilized.

Ultra High Throughput Screening (uHTS) : A screening rate of 100,000 assays per day. [IUPAC Combinatorial Chemistry]

Narrower term: [cell- based uHTS](#); **Broader term:** [High Throughput Screening HTS](#)

virtual screening: [In silico & molecular modeling](#)

whole embryo assays: Phylonix is developing a family of zebra fish bioassays for drug discovery and screening. In addition to a number of visual assays performed in the transparent embryo, we are screening chemical libraries using a robotic liquid handling workstation and a 96-well microplate reader. One hundred thousand compounds can easily be screened in 60 days. Current formats include angiogenesis, apoptosis, and organ toxicity. Whole embryo assays are more informative than cells and more convenient than mice. "Whole Embryo Assays" Dr. Catherine Willett, Senior Scientist, Phylonix, Inc [Animal Models: Genomics on Target Nov. 20- 21, 2002, Boston, MA](#)

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[Alpha glossary index](#)

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